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| 09/647,924 | 10/31/2000 | Hiroyoshi Hidaka | 198323US0PCT | 6890 |

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| EXAMINER |
|---|
| FRIEND, TOMAS H F |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1639 | |

DATE MAILED: 12/30/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary<br>file copy | Application No.<br>09/647,924 | Applicant(s)<br>HIDAKA ET AL. | |
|---|---|---|---|
| | Examiner<br>Tomas Friend | Art Unit<br>1639 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *2-14* is/are pending in the application.

4a) Of the above claim(s) *14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

# Detailed Action

## Change of Art Unit Designation

**Please note:** The Art Unit location of this application in the PTO has changed from Art Unit 1627 to Art Unit 1639. To aid in matching papers to this application, all further correspondence regarding this application should be directed to **Group Art Unit 1639**.

## Status of the Application

Receipt is acknowledged of a response to an office action with amendment on 08 May 2002 (Paper No. 8). A response to an election of species requirement was received on 03 September 2002 (Paper No. 11) and a response to a notice of non-responsive amendment was received on 11 October 2002 (Paper No. 13). An information disclosure statement was received on 14 June 2002 (Paper No. 9).

## Status of the Claims

Claims 1-4 were pending in the application. Claim 1 was cancelled and new claims 5-14 were added by amendment in Paper No. 8. Claim 14 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 11.

Claims 2-13 are pending and examined on their merits.

## Response to Restriction and Election of Species with Traverse

Applicant's election with traverse of (A) serum albumin as species of antigenic substance; (b) glutaraldehyde as species of chemical cross-linker; and (C) drug A as species of drug in Paper Nos. 11 and 13 is acknowledged. The traversal is on the ground(s) that the examiner has

not provided adequate evidence or reason that the species represent patentably distinct inventions or that examining all of the species would be a serious search burden. This is not found persuasive because the examiner indicated in the election of species requirement that:

*"The species listed above do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, the species lack the same or corresponding special technical features for the following reasons: the species have different chemical structures with different chemical, physical, and biological (e.g. pharmacological and immunological) properties."* Searching the different species requires different structure, key word, and/or class/subclass searches, for example.

The requirement is still deemed proper and is therefore made FINAL.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

**Withdrawn Rejections/Objections**

1. All rejections of claim 1 are withdrawn in response to applicants' cancellation of the claims.

2. The rejections of claims 2-4 under 35 U.S.C. 112, second paragraph, made in the office action mailed 08 February 2002 (Paper No. 6) are withdrawn.

3. The objections to the specification made in Paper No. 6 are withdrawn in response to applicants' amendment.

4. The objection to claim 4 as being an improper dependent claim is withdrawn in response to applicants' amendment.

**Maintained Rejections**

The statutory basis for each of the following rejections may be found in a prior office action.

**Maintained Rejections – 35 U.S.C. 112, first paragraph**

5. Claims 2-4 remain rejected and new claims 5-13 are rejected under 35 U.S.C. 112, first paragraph (scope of enablement) for reasons made of record in paper No. 6.

Applicants argue that the present specification contains [1] preferred drugs to be used; [2] guidance for the selection of cross-linkers; [3] detailed description of antigenic substances; [4] explanations of how to make drug-antigenic substance conjugates; and [5] a screening method to enable one skilled in the art to assess the effectiveness of the compounds made.

Applicants' arguments have been fully considered but they are not persuasive.

The arguments provided do not address the factors cited by the examiner in Paper No. 6, which were used as a basis for determining whether undue experimentation would be required by one skilled in the art to use the claimed method commensurate in scope with the claims. The scope of the claims includes in the method any non-antigenic drug substance whatsoever, including sugars, small peptides, opioids, benzodiazepines, metal ions, steroids, and aspirin, for example. These molecules have diverse chemical structures and bind to a wide variety of proteins at widely diverse binding site structures, which are also encompassed in the claimed method. The antigenic substances encompassed by the method share no common structural characteristics and share only the functional characteristic of causing the production of antibodies in an animal capable of mounting an immune response. Consequently, the variety of structures is enormous and includes peptidomimetics, peptides, and peptides conjugated with virtually any other type of molecule including carbohydrates and small organic molecules, for example.

Providing lists of preferred drugs, chemical cross-linkers, antigenic substances, and general methods for chemically cross-linking drugs to antigenic substances does not enable one skilled in the art to use the claimed invention commensurate in scope with the claims. The level of guidance provided in the specification would not allow one to predictably generate probes that maintain the ability of the parent drug to bind a protein target in the same way as the parent drug alone. It is well known in the art that even a minor change to the structure of a drug most often renders the drug ineffective or substantially less effective than the parent molecule. No guidance

is provided in the specification that would allow one skilled in the art to predictably synthesize probes that have the same protein binding activity as drug from which they are made.

## New Grounds of Rejection

The statutory basis for each of the following rejections not found below may be found in a prior office action.

## New Grounds of Rejection – 35 U.S.C. 112, first paragraph

6. Claims 2-13 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (written description).

Applicants claim a method for detecting a gene (that encodes) a drug-targeted protein. There are no functional or structural limitations with respect to the drug, only a limitation that the drug not be immunogenic. There are no limitations with respect to the protein to be targeted with respect to structure, function, or location within the cell in the native state (i.e. intracellular, extracellular, nuclear, transmembrane, etc.

The method uses phage display to express a cDNA library, using a membrane to capture phage from plated phage cultures, and contacting the membrane with a drug that is covalently attached to a molecule that can be bound by an antibody, which is used for detection.

To satisfy the written description requirement, applicants must describe the invention in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Applicants have provided in the specification a single example involving an anti-cancer drug, BSA as the antigenic substance, and Sulfo-SMPB as the cross-linking agent.

It is a well-established fact in the art of pharmaceuticals, that even a small change in the structure of a drug often renders the drug unable to bind its corresponding protein target(s). Accordingly, the predictability in the art is low that one would be able to covalently attach a

moiety (large enough to be antigenic) to a drug without altering its binding to a drug target. Consequently, in order to demonstrate possession of the full scope of the claimed method, applicants must provide representative examples that would reasonable convey to one skilled in the art that applicants, at the time of filing, possessed a method that would work with most drug/crosslinker/antigenic substance combinations. The single example provided in the specification is insufficient to demonstrate possession of the full scope of the clamed method.

**New Grounds of Rejection – 35 U.S.C. 112, second paragraph**

7. Claims 2-13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. It is not clear how claim 3 further limits new claim 5. Claim 3 recites the limitation that the cDNA library of claim 5 is contained in a phage vector. Claim 5 recites a method in which protein is expressed from a cDNA expression library that forms phage plaques. It appears that the "*phage vector*" limitation in claim 3 is inherent in claim 5, from which claim 3 depends.

B. In claim 5, it is not clear if "*gene of a drug-targeted protein*" is to be interpreted as "*gene encoding a drug-targeted protein.*"

C. In claim 5, the phrase "*contacting a membrane to a phage plaque, with a host cell, expressing protein from a cDNA expression library*" is confusing, in part because of grammatical errors. It is not clear if "*contacting... to*" is intended to mean "*contacting...with.*" The relationships between "*a host cell*" and a plaque, a membrane, and contacting are not clear. A host cell, for example, cannot express an entire library but the claim appears to indicate that it does.

D. Claim 5 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: [1] plating a cDNA phage display culture in such a way as to form phage plaques, the attachment of phage to the membrane as a result of contacting the membrane with the plaque, and [3] removing the membrane from its contact with a phage plaque

(and host cell?) before contacting the membrane with probe. It appears from the claim that only a single plaque is required, which is contrary to the method disclosed in the specification.

E. In claim 5, it is not clear if the probe-bound phage is still on the membrane when it is detected or the source of the gene sequence to be determined. It appears form the claim language that the entire cDNA library is contained within a single phage.

**New Grounds of Rejection – 35 U.S.C. 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 2-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Sparks et al. WO 96/31625 (October 1996).

The Sparks et al. reference discloses a method of identifying polypeptides by means of a recognition unit-based screen (abstract). Page 25 of the reference, lines 24-34, discloses a method comprising (a) contacting a multivalent recognition unit complex, which complex (i) avidin or streptavidin (antigenic substance) and (ii) biotinylated recognition units (i.e. biotinylated drug), with a plurality of polypeptides from a cDNA expression library, in which the recognition unit is a peptide having the range of 6 to 60 amino acid residues; and (b) identifying a polypeptide having a selective binding affinity for said recognition unit complex. Page 32, lines 25-32, defines a "*recognition unit*" as "*any molecule having selective affinity for the functional domain of the target molecule and, preferably, having a molecular weight of up to about 20,000 daltons.*" Page 33, lines 1-3, discloses that the recognition unit may be "*a peptide, a carbohydrate, a nucleoside, an oligonucleotide, any small synthetic molecule, or a natural product.*" Page 33, lines 30-32, discloses that a drug may be used as a recognition unit. Page 38, lines 2-11, discloses that the expression system used may use bacteriophages to express cDNA from a particular organism, tissue type, developmental stage, or disease condition or stage. Page 39, lines 28-33, discloses that prior to contacting the recognition unit, the polypeptides can be

transferred to a solid support such as a nitrocellulose filter. Page 77, lines 3-37, disclose an example in which mouse embryo cDNA was expressed from a λExlox expression vector. Plaques (on agar plates) were contacted with IPTG soaked filters. The filters were marked, removed from the plaques, washed, blocked, and incubated with a peptide recognition unit complexed with streptavidin-alkaline phosphatase. Page 44, lines 34-37, discloses that a recognition unit may alternatively be chemically cross-linked to BSA using known cross-linking reagents. The use of a human cDNA expression library is disclosed, for example, in claim 37. Page 79, lines 4-33, discloses the isolation and sequence determination of positively identified phage clones that encode proteins that bind to the recognition unit complex. Accordingly, the Sparks et al. reference anticipates present claims 5, 2-4, 6-8, 11, and 12.

**New Grounds of Rejection – 35 U.S.C. 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 2-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sparks et al. WO 96/31625 (October 1996) and Hutchens et al. U.S. Patent 5,161,615 November 1992.

The teaching of the Sparks et al. reference are described in the corresponding rejection under 35 U.S.C. 102(b) and are incorporated herein in their entirety.

The Sparks et al. reference does not explicitly teach the use of human brain or placenta cDNA libraries or the use of glutaraldehyde or other specified chemical cross-linking agents.

It would have been well within the abilities of one of ordinary skill in the art at the time that the invention was made to select a cDNA library from any desired cell line. In this instance, one of ordinary skill would have been motivated to select a human brain cDNA to search for proteins that bind to a drug used in the treatment of a brain disease such a Parkinson's disease or Alzheimer's disease. One would have been motivated to human placenta cDNA when a drug is suspected to bind a protein in the placenta or is suspected of being transported through the

placenta (to the fetus) for example. One would have had a reasonable expectation for success because the synthesis of cDNA libraries from any tissue was routine in the art at the time.

The Hutchens et al. reference teaches that glutaraldehyde, for example, was a commonly used chemical cross-linking agent used to cross-link organic molecules (column 3, lines 32-39). It would have been obvious to one of ordinary skill in the art at the time that the invention was made to use glutaraldehyde, for example, as a chemical cross-linking agent. One would have been motivated to do so because this reagent was commonly used at the time as a chemical cross-linking agent and the Sparks et al. reference teaches one to use "*known cross-linking reagents*." One would have had a reasonable expectation for success because glutaraldehyde was in common use as an organic chemical cross-linking agent at the time.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Tomas Friend** at telephone number **(703) 308-4548**. The examiner's normal schedule is four, ten-hour days per week including Saturdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

ANDREW WANG
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Tomas Friend, Ph.D.
19 December 2002